OTS: 60-41,644

JPRS: 5886

17 October 1960

THE THERAPY OF CARDIAC INSUFFICIENCY WITH CONVALLATOXIN

By V. I. Chernov

- USSR -

Distributed by:

OFFICE OF TECHNICAL SERVICES
U. S. DEPARTMENT OF COMMERCE
WASHINGTON 25, D. C.

~~Price: $0.75~~

U. S. JOINT PUBLICATIONS RESEARCH SERVICE
205 EAST 42nd STREET, SUITE 300
NEW YORK 17, N. Y.

JPRS: 5886
CSO: 4884-N

THE THERAPY OF CARDIAC INSUFFICIENCY WITH CONVALLATOXIN

[Following is the translation of an article by V. I. Chernov entitled "Lecheniye Serdechnoy Nedostatochnosti Konvallotoksinom" (English version above) in Terapevticheskiy Arkhiv (Therapeutic Archives), Vol. 32, No. 5, Moscow 1960, pages 26-34)].

From the hospital of propedeutic therapy (Head -- Docent V. I. Chernov) of the therapeutic faculty of L'vov Medical Institute

In recent years many glycosides with a strophanthin-like effect have been proposed for the treatment of cardiac insufficiency (eryside [cardiac glycoside isolated from Erysimum canescens], erysimin corglycon [glycoside from Convallaria majalis, etc.]). In the publications of D. D. Yablokov and A. M. Voronov, D. D. Yablokov, M. I. Shubov, I. I. Sivkov, V. E. Golavskiy and G. O. Badalyan a good therapeutic effect of these agents is noted. However, in evaluating the therapeutic effect of new glycosides they are not always objectively compared with strophanthin. Nevertheless, the comparative characteristics are important so as to be able to take into consideration the actual significance

of the preparations being proposed, to assure the best selection of them for the treatment of cardiovascular diseases (A. P. Pomerantsev, V. I. Chernov, V. Kh. Vasilenko and V. N. Vinogradov and others).

Of the various convallaria preparations used for treatment the crystalline glycoside convallatoxin deserves attention; this was obtained in 1929 by Karrer from the flowers and leaves of the plant of the same name. In its chemical characteristics, which were given by Tesche and Haupt, convallatoxin ($C_{29}H_{42}O_{12}$) is similar to strophanthin but is distinguished from it by its sugar residue. Lutenbach and de Luneau (we are quoting from Dursch) isolated K-strophanthidin from convallatoxin. According to Baker, the therapeutic effect of convallatoxin is about the same as the effect of strophanthin.

The activity of convallatoxin, which has been made clear in experiments on frogs, amounts to 3,000,000-3,500,000 FD per gram according to the data of Fromherz and Welsch. It has been determined that one gram of convallatoxin contains 75,000 frog units or about 10,600 cat units, whereas one gram of strophanthin contains 40,000 frog units and 6,500 cat units (M. D. Moshkovskiy). Therefore, the biological activity of convallatoxin is greater than all the other cardiac

glycosides known (F. I. Onitsev, Schmitz).

In the Soviet literature there are practically no studies devoted to the clinical evaluation of this preparation unless we consider the report by B. Ye. Votchal, where it is mentioned that "according to the existing sparse data we can tentatively divide the preparations in the following order with respect to decreasing effectiveness: strophanthin, convallatoxin, corglycon, eryside, and cymarin [from Apocynum cannabinum]".

Abroad, some authors evaluate the therapeutic effect of convallatoxin highly. Uhlenbruck and Schmitz, for example, believe that convallatoxin is similar to strophanthin but acts more selectively on the right heart.

We set before ourselves the problem of evaluating the therapeutic qualities of convallatoxin compared with strophanthin and making the dosage of the preparation more exact. There were 58 patients with severe forms of circulatory disorders (degrees IIB and III) under our observation, including 25 men and 33 women of different ages. The circulatory insufficiency in 19 patients was brought about by myocardial disease; in the other 39 patients, by rheumatic valve defects of the heart, whereby in 13 there was an active rheumatic process. In connection with this, the patients of the last group

were given hormone therapy simultaneously with the convallatoxin (ACTH, less often cortisone), pyramidon, sodium salicylate, etc. The circulatory insufficiency in 30 patients was complicated by auricular fibrillation; in four, by extresystoles; in four, by incomplete A.V. block; in one, by a complete block; and in two patients, by paroxysmal tachycardia.

In all patients, before and after treatment, and in many during treatment consideration was given to the frequency and rate of cardiac contractions, the number of respirations, the percussion and auscultatory data of the heart and lungs, the 24-hour diuresis, body weight, size of the liver, the arterial and venous pressure, the circulation time, the electrocardiographic data, oscillography, ballistocardiography and fluoroscopy.

Convallatoxin was given intravenously in 10-15 cubic centimeters of 40 percent glucose solution in a dose of 0.15 milligram and occasionally, in a dose of 0.1 milligram twice a day. We were convinced of the expediency of giving the injection twice in studying the therapeutic effectiveness of other glycosides also -- strophanthin, corglycon and periplocin. It should be kept in mind that individual sensitivity of the patients to glycosides is different; therefore, considerable

caution is needed in the dosage. In order to avoid any side-effects it is best to begin treatment with a sub-threshold therapeutic and supportive dose. In 1936, Edens and Auer in 1938 found the basic principle of strophanthin treatment: the more severe the decompensation the smaller the dose of the preparation should be. Our many years of observation of a large number of cardiac patients showed that the double injection of glycosides during the day more rapidly eliminates their decompensation. Thereby, the treatment period is considerably shortened compared with a single injection of the preparation. As a result, the possibility has been created of shifting over to the ordinary definitive stage of digitalis treatment comparatively more quickly. The double injection of glycosides, by giving a more rapid therapeutic effect, at the same time reduces the possibility of the appearance of toxic properties of the preparation.

We are presenting an observation as an example.

Patient Kh, age 32, was admitted to the hospital in a serious condition. He complained of constant shortness of breath, palpitation, cough; he had pedal edema, and his abdomen was enlarged. At the age of 28 he had had rheumatic polyarthritis after a sore throat. Occasionally he noted shortness of breath which

increased for the past two years.

Objectively: there was pronounced shortness of breath, 32 respirations a minute, cyanosis, ascites, peripheral edema. The pulse was 120 beats a minute and was arrhythmic (there was a pulse deficit of 30 beats a minute), small and soft. The heart was enlarged in all directions; its transverse diameter was 18 centimeters; there was a systolic murmur at the apex. There were hypostatic râles in the lungs. The liver projected to seven centimeters below the rib cage. The blood pressure was 105/70 millimeters of mercury; the circulation time, 30 seconds. On electrocardiography: there was auricular fibrillation, tachycardia, and a right axis deviation. On the oscillogram there were hardly noticeable irregular oscillations.

The clinical diagnosis was mitral valve defect with predominance of stenosis; there was a cardiovascular insufficiency, IIB in degree.

Convallatoxin was prescribed in a dose of 0.15 milligram twice a day. On the fourth day of treatment the patient's condition improved considerably: there was a reduction in shortness of breath, in the pulse rate and in the pulse deficit, and the liver became smaller. After one cubic centimeter of mersalyl a diuresis of 2.3 liters began. A shift was made to strophanthin

over the course of five days in the same doses, and there was no difference found by comparison with convallatoxin. Subsequent injection of convallatoxin for five days produced a definite improvement in the patient's condition. The shortness of breath disappeared (the number of respirations was 18 per minute), as did also the edema, stasis in the lungs; the palpitation stopped; sleep became quiet; the pulse was 60 beats a minute at rest and arrhythmic. The liver was enlarged by only two centimeters. The venous pressure was 130 millimeters of water. The circulation time was 25 seconds. On the oscillogram there were definite oscillations up to one centimeter. The ballistocardiogram showed first degree disturbance according to Brown. The patient was discharged in good condition.

In this case the use of convallatoxin eliminated the severe form of decompensation. The rapid and quite definite therapeutic effect is explained by the fact that there was no marked change in the cardiac muscle in this patient. With the improvement of the metabolic processes in the myocardium under the influence of the glycoside the functional capacity of the muscle was improved (Fig. 1).

The expediency of repeated intravenous injections

of strophanthin for 24 hours in the presence of severe decompensation and pronounced edema have been emphasized by Edens, Auer, V. N. Vinogradov and others. They recommend the injection of strophanthin in a dose of 0.1 or 0.15 milligram two or three times a day. Small doses of strophanthin can be used for weeks and months, because the danger of habituation to strophanthin and of a cumulative effect from these doses is excluded. Strophanthin and convallatoxin are eliminated from the body after six-eight hours.

It should be stated that the therapeutic action of glycosides, including convallatoxin is not always effective. This has been observed in the presence of deep-seated changes in the cardiac muscle. In evaluating the effect of glycosides the age of the patient, duration of the disease, causes producing the decompensation as well as the pre-existing frequency and duration of the decompensation are important. The more frequent and more prolonged the decompensation the less effective the treatment results are.

Patient Ye., age 67. Clinical diagnosis: arterio-sclerotic myocardial fibrosis, auricular fibrillation, hypertension. There was a circulatory insufficiency, IIB. He was admitted to the hospital in a serious

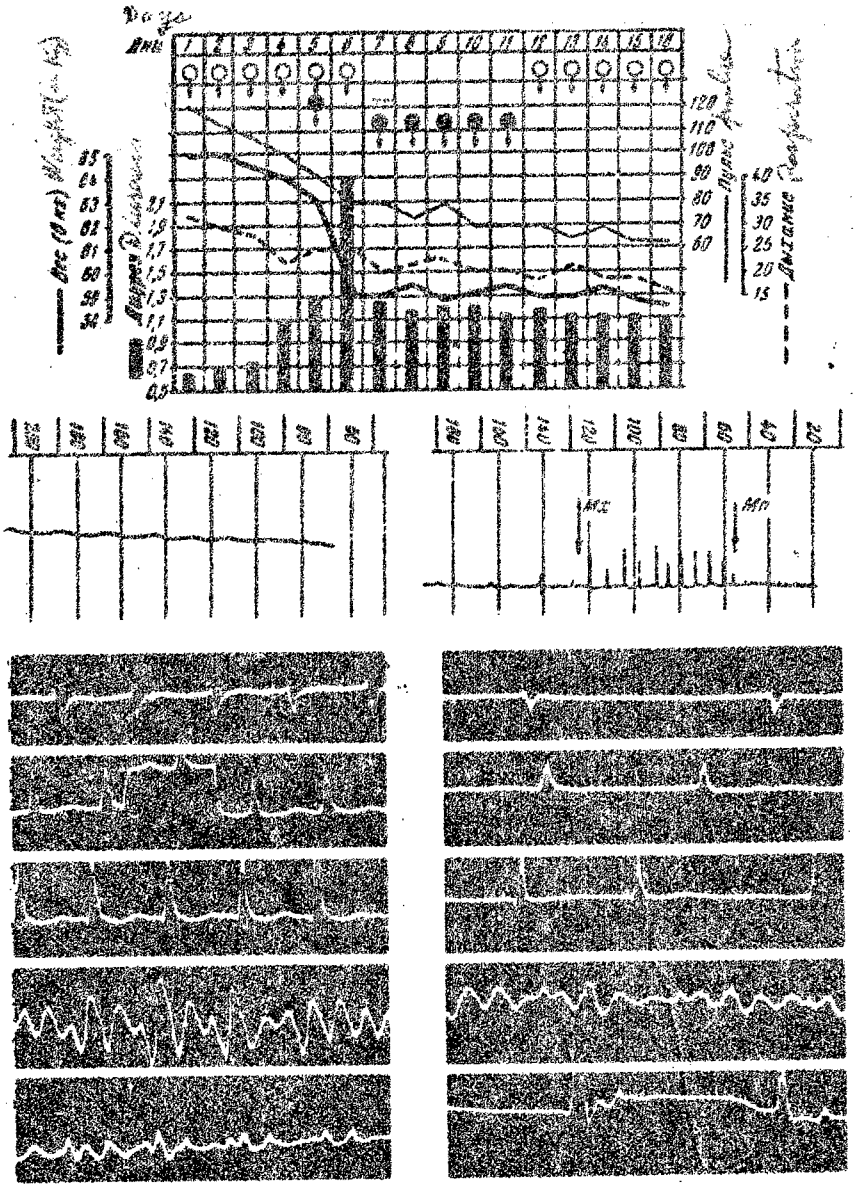

Fig. 1. Results of Convallatoxin and Strophanthin Treatment of Patient Kh. The white circles with the arrows represent convallatoxin; the white with the black circles, K-strophanthin; the black circles, mersalyl. Shown are the oscillogram, electrocardiogram (in three leads), ballistocardiogram with P wave superposed, and the electrosphygmogram.

At left, before treatment. On the right, after treatment.

condition with constant dyspnea, cyanosis, edema of the lower extremities, stasis in the lungs and liver. On X-ray examination: transverse diameter of the heart was 18.5 centimeters. Electrocardiographically the fast auricular fibrillation was noted with a pulse rate of 120 beats a minute. On the oscillogram -- Mx was 175; Mn -- 120; the oscillations were up to 0.8 centimeter. On the ballistocardiogram there was a decrease in the size of the waves of the systolic complex, tall L waves, and a second-degree disturbance according to Brown. Convallatoxin was prescribed in a dose of 0.15 milligram twice a day.

After seven days of treatment a notable improvement occurred. Subsequent treatment with strophanthin in a dose of 0.15 milligram twice a day for seven days did not show any particular advantages. Afterwards, convallatoxin was again prescribed for five days. The patient's condition improved considerably. After treatment the oscillogram showed the following: Mx -- 180; Mn -- 80; there was a pronounced decrease in the diastolic pressure. The pulse was 55 at rest. On the electrocardiogram there were signs of chronic myocardial ischemia (depressed ST_1, ST_2 with a negative T in the first lead). On the ballistocardiogram after treatment

there were reduced waves in the systolic complex and reduced diastolic L waves (Fig. 2).

As in the case of the previous patient, convallatoxin showed a distinct subjective and clinical improvement. However, the ballistocardiographic, electrocardiographic and oscillographic investigations showed pronounced myocardial changes in the patient, a chronic coronary insufficiency in connection with arteriosclerotic myocardial fibrosis and coronary sclerosis.

A study of the effect of convallatoxin on the atrioventricular conduction is of clinical interest. Delayed conduction serves as an indication for reducing the dosage of the preparation in order to avoid partial A-V block, whereby treatment has to be stopped; this is extremely undesirable for patients with severe cardiac insufficiency. Partial A-V block can be the result of coronary insufficiency and therefore of poor nutrition of the conduction system of the heart. In these cases, the glycosides, by contributing to the elimination of cardiac insufficiency, can simultaneously eliminate the conduction disturbance. A conclusion of this kind has been confirmed by observations on two patients with severe decompensation against the background of an active rheumatic process, complicated by mitral-aortic

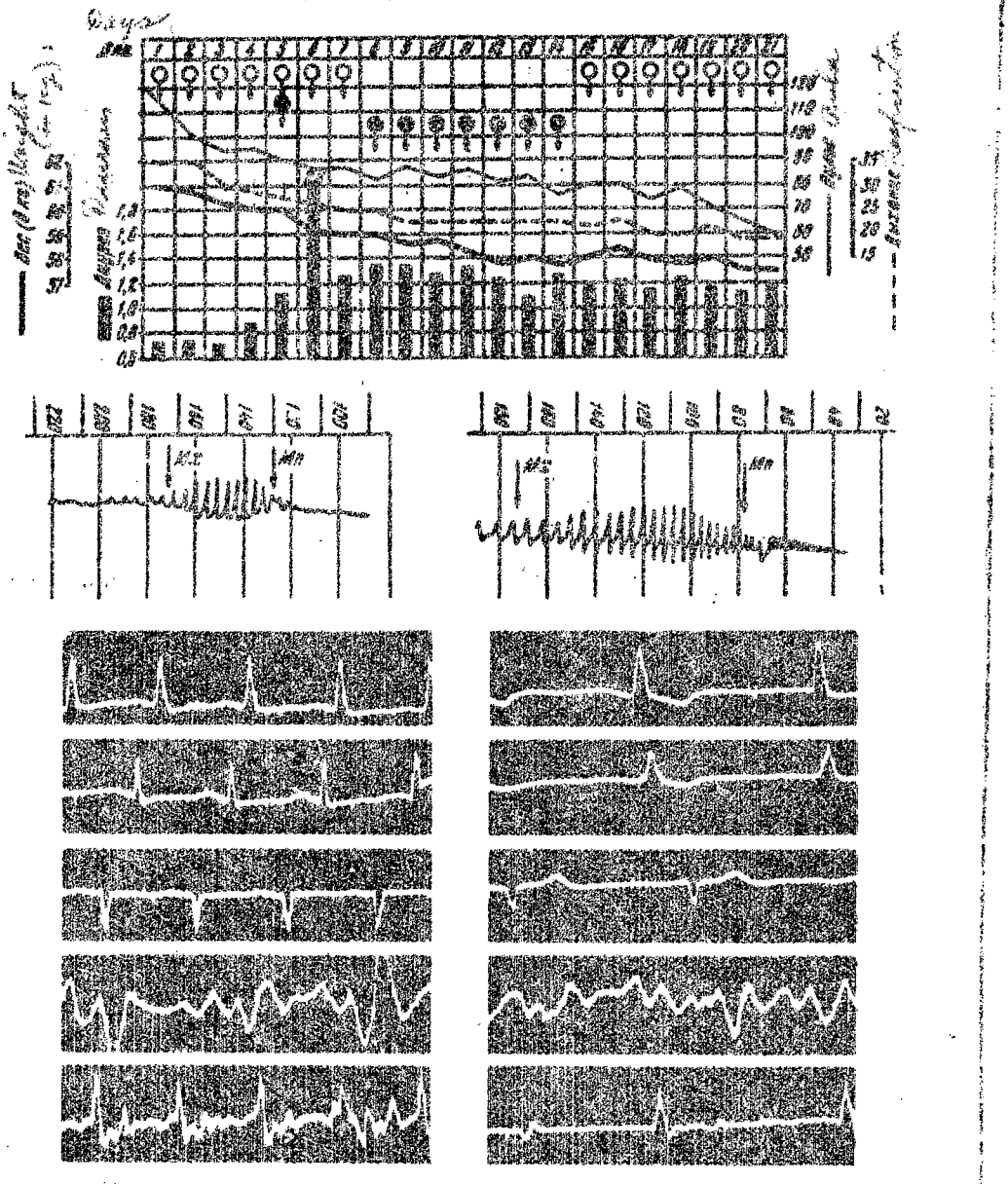

Fig. 2. Results of Convallatoxin and Strophanthin Treatment of Patient Ye.

The key is the same as for Fig. 1.

Shown are oscillogram, electrocardiogram (in three leads), ballistocardiogram with P wave superposed, and electrosphygmogram.

On the left, before treatment; on the right, after treatment.

involvement of the cardiac valves. Treatment of these patients with cortisone and convallatoxin contributes to the restoration of the disturbed conduction, as a result of which the patient's condition notably improved.

The situation is different when partial A-V block has been demonstrated against the background of a burned-out rheumatic process, an existing valve defect and severe decompensation. In such cases, it is better to prescribe ordinary doses of strophanthin (A. M. Sigal) or, in our opinion, convallatoxin. These preparations, without aggravating the partial A-V block, are capable of bringing the patient out of the state of decompensation with preservation of the contractile properties of the cardiac muscle.

We are presenting a case history as an example.

Patient Sh., age 21. Clinical diagnosis: mitral-aortic valve defect. Circulatory disturbance, IIB-III, complained of constant dyspnea, pains in the cardiac region, attacks of palpitation and edema. In recent years, he had been frequently treated in the hospital for cardiac decompensation.

On objective examination the following were found: the heart was enlarged to the left by 3.5 centimeters; its diameter was 17 centimeters. Over the cardiac apex

there was a systolic and diastolic murmur; over the aorta, a diastolic murmur. The pulse was 80 beats a minute, small, soft, with rare extrasystoles. The blood pressure was 95/50 millimeters of mercury; the venous pressure was 160 millimeters of water. The circulation time was 40 seconds. In the lungs there were hypostatic rales. The respiratory rate was 26 a minute. The liver was eight centimeters below the costal margin and of moderate density, and was tender on palpation. There was pronounced edema of the lower extremities and lumbar area.

The patient was given convallatoxin, first in a dose of 0.1 milligram and then in a dose of 0.15 milligram twice a day. The diuresis of 600 cubic centimeters increased to 1200 cc. on the third day of treatment. By the sixth day of treatment edema and dyspnea had decreased considerably. The liver had become four centimeters smaller. For six days treatment was given with strophanthin in a dose of 0.15 milligram twice a day; there was no noticeable difference found by comparison with convallatoxin. During the next four days convallatoxin was used. The dyspnea practically did not trouble the patient; the pains in the cardiac region stopped. The liver was three centimeters below the costal margin. The pulse was 70 beats a minute, and

respirations were 19 a minute. The blood pressure was 100/50 millimeters of mercury; the venous pressure, 140 millimeters of water; the circulation time was 25 seconds. On the oscillogram there was an increase in the oscillations. On the electrocardiogram there was a partial A-V block (P-Q = 0.25 second), which remained after treatment. The use of 0.75 cc. of atropine for five days did not improve the conduction. Before treatment a certain depression of the ST segment, flattening of T_1, negative T_2 and T_3 waves were found. After treatment, T_1 was unchanged, T_2 became more positive; T_3 was unchanged; this may serve as a sign of chronic myocardial ischemia. The ballistocardiographic changes (pronounced reduction in the waves of the systolic complex, confluent HS waves, tall I waves) remained the same as before treatment (Fig. 3).

In this case, clinical improvement occurred under the influence of treatment; however, the electrocardiographic data, as well as the data of ballistocardiography and oscillography were evidence of considerable changes in the cardiac muscle. A month after discharge the patient again was admitted to the hospital with the previous signs of decompensation.

In the study of the electrocardiograms attention

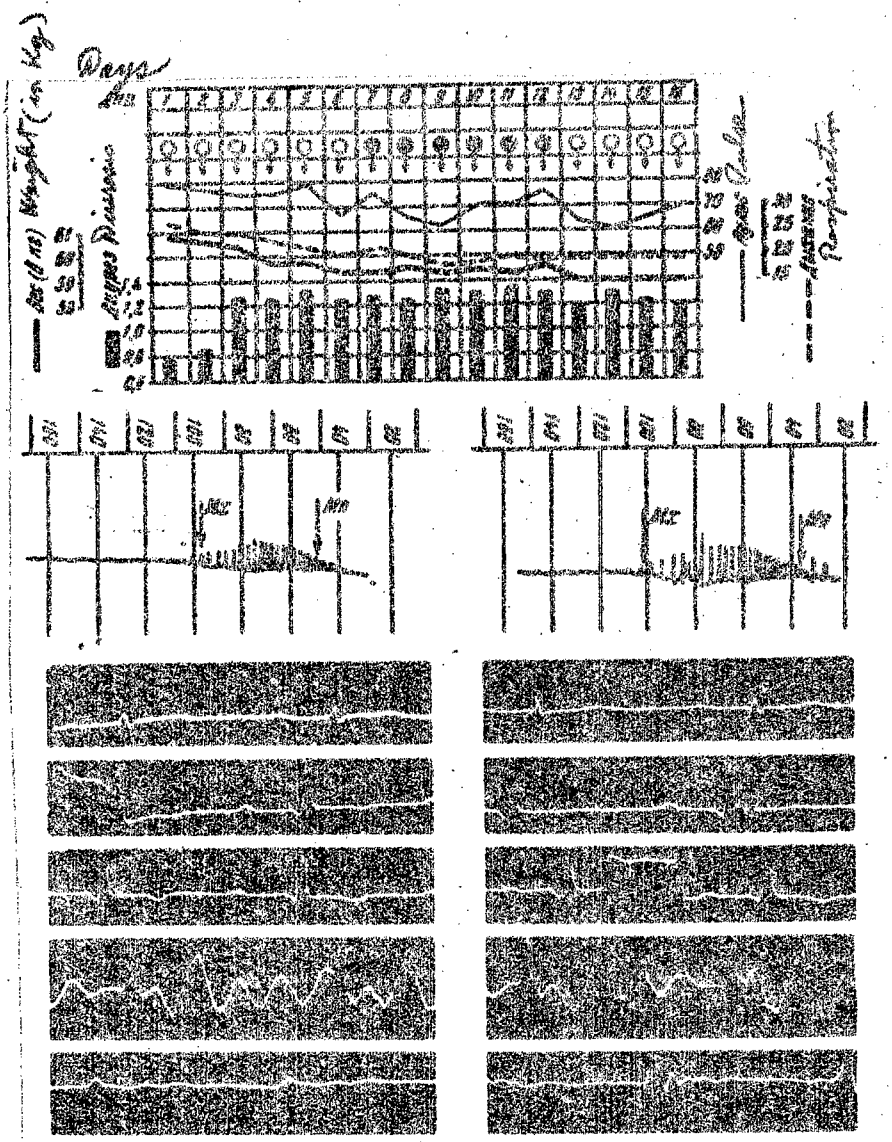

Fig. 5. Results of Convallatoxin and Strophanthin Treatment of Patient Sh. The key is the same as for Fig. 1. Shown are the oscillogram, electrocardiogram (with three leads), ballistocardiogram with P wave superposed, and electrosphygmogram.

On the left, before treatment; on the right, after treatment.

was directed to the slowing of the cardiac rate even two to three minutes after the intravenous injection of convallatoxin. Lengthening of the R-R varied and depended on the original condition of the cardiac muscle. Convallatoxin, like strophanthin, did not exert any influence on the duration of the P-Q interval, which is an advantage of these preparations over digitalis.

The injection of convallatoxin usually produced a shortening of the Q-T interval and a corresponding reduction of the systolic index. These changes should be regarded as signs of a favorable influence of the preparation on the contractile power of the cardiac muscle, particularly on systole. Simultaneously with the shortening of systole diastole was lengthened because of the lengthening in the T-P segment. Convallatoxin did not exert any noticeable effect on the P, R, QRS waves. On some of the electrocardiograms following convallatoxin treatment a hitherto depressed (below the isoelectric line) S-T interval became more positive, and a previously indefinite T wave appeared; sometimes there was a shift of it from negative to positive. However, we could not find any regular changes in the T wave. The conglomeration of changes on the electrocardiogram (rate, conduction, position of the

terminal portion of the ventricular complex) can characterize convallatoxin as a glycoside similar to strophanthin.

Making extensive use of the readings of a ballistocardiograph with an electromagnetic feeler in our observations, we took into consideration the merits and defects of this method. Ballistocardiography, permitting the recording of various disturbances in the work of the cardiac muscle, does not show the anatomic nature of these disturbances. The defect of the method is also the fact that in the same patient the ballistocardiogram has to be recorded several times in order to draw conclusions on the basis of repeated uniform results (Starr; Kodejszko and Czernik). Therefore, it should be regarded only as a valuable element in the comprehensive investigation of cardiac patients.

Observations have shown that in those cases where the electrocardiography revealed signs of involvement or hypoxia of the myocardium usually various disturbances in the ballistic curves were recorded on the ballistocardiograms. The most frequent type of change was an increase in the height of the L and H waves, a reduction in the amplitude of the J wave and an absence of the I wave. Thus, in the case of bicuspid valve defects tall L

and other diastolic waves were found (sometimes M) as well as a great amplitude of the H waves, which at times assumed a biphasic character.

In the case of aortic insufficiency with decompensation tall diastolic waves with an indefinite H, J, K complex were recorded. In patients with auricular fibrillation the initial part of the systolic complex not uncommonly was changed in an indefinite manner.

In 33 of our patients before treatment the ballistocardiograms showed third-to-fourth degree disturbances according to Brown. After treatment, they remained as before. These were people who had been sick a long time, with repeated histories of decompensation. They were discharged from the hospital improved or without any effect. In the remaining 23 patients who were given ballistocardiographic examinations changes of second-and-third degree were noted. The effective treatment restored the normal picture in 19 patients. In this group, the duration of the disease was comparatively small, and decompensation was noted only rarely in the past.

The results of treatment of 58 patients with convallatoxin were the following. Of 32 patients with decompensation of the IIB degree a considerable

improvement occurred in 12; improvement, in 15; no effect, in five. In the group of 26 patients with third-degree decompensation a considerable improvement occurred in six; improvement, in 10; in eight treatment did not give any effect, and two died.

Of 18 patients in whom a considerable improvement was noted, 12 suffered from mitral valve defects and six, from arteriosclerotic myocardial fibrosis, including cor pulmonale in two. Of 25 patients discharged improved 14 had a mitral valve defect; four had a mitral-aortic valve defect; four, arteriosclerotic myocardial fibrosis; and three, cor pulmonale.

It should be noted that among 30 patients with circulatory insufficiency complicated by auricular fibrillation of different etiologies, a definite improvement was noted in 25 after convallatoxin treatment: the fast form of arrhythmia changed into a slow form; in five patients with a slow auricular fibrillation convallatoxin contributed to the occurrence of a relative compensation. In four patients with extrasystoles the normal rhythm was recovered in two. In four patients with incomplete A-V block, two patients among them suffered from recurrent endocarditis with lesions on the mitral and aortic valves; treatment with cortisone

and convallatoxin led to a shortening of the P-Q interval from 0.26 second to normal. In two patients with cardiovascular insufficiency against the background of a mitral valve defect and attacks of paroxysmal tachycardia the attacks were eliminated after the first infusion of convallatoxin in a dose of 0.2 milligram and were not repeated subsequently. The use of convallatoxin did not show any effect in 11 patients.

Conclusions

1. Treatment of cardiac insufficiency with convallatoxin confirms the statements made by a number of clinicians to the effect that this glycoside is very similar to strophanthin in its effect.

2. The observations constitute evidence of the expediency of a double injection of convallatoxin (and other glycosides) in a dose of 0.1-0.15 milligram during the day, since this method of treatment shortens the treatment time without producing any side-effects or cumulative effect in the process. A single dose per day lengthens the treatment and creates the impression, sometimes, that the preparation is not very effective.

3. In evaluating the therapeutic effect of convallatoxin (and other glycosides) the control exercised by means of ballistocardiography, electrocardiography

and oscillography, making it possible to judge the treatment results more objectively, are of importance. Changes in the electrocardiograms and ballistocardiograms regularly reflect the pathological processes and functional disturbances in the heart in the presence of circulatory insufficiency and graphically demonstrate the changes which occur as the result of treatment.

4. Clinical observations make it possible to consider that convallatoxin, like strophanthin, is indicated for decompensation brought about by mitral valve defects. The results of treatment were unstable, where the course of the disease was complicated by endomyocarditis. The therapeutic effect was not always adequate in myocardial fibrosis, to which pulmonary emphysema and pulmonary fibrosis contributed, or in aortic lesions. Convallatoxin, like strophanthin, did not have any effect in the case of irreversible changes in the cardiac muscle.

5. The preliminary data indicate that convallatoxin deserves a detailed clinical study by virtue of its therapeutic effect.

Bibliography

1. Badalyan, G. O. Sov. med. / Soviet Medicine 7, 1958, No. 2, page 44.

2. Vinogradov, V. N., Ter. arkh /Therapeutic Archives_7, 1957, No. 7, page 3.
3. Votchal, B. Ye. Opus cit, 1958, No. 9, page 94.
4. Golavskiy, V. E. Klin. med. /Clinical Medicine_7, 1957, No. 3, page 50.
5. Moshkovskiy, M. D., "Drugs". Moscow, 1958.
6. Onitsev, P. I., Farmakol. i toksikol. /Pharmacology and Toxicology_7 , 1943, No. 6, page 30.
7. Sivkov, I. I., Sov. med., 1952, No. 8, page 26.
8. Sigal, A. M., "Digitalis and Its Therapeutic Use". Moscow, 1956.
9. Chernov, V. I., Proceedings of the Seventh Congress Of Internists of the UkrSSR. Kiev, 1957, page 236.
10. Shubov, M. I., Ter. arkh., 1951, No. 2, page 59.
11. Yablokov, D. D., Opus cit., 1950, No. 3, page 86.
12. Yablokov, D. D., Voronova, A. M., in the book: "New Medicinal Plants of Siberia, Their Therapeutic Preparations and Application". Novosibirsk, 1949, No. 3, page 201.
13. Auer, A., Ztschr. f. arztl. Fortbild, 1938, Vol. 35, page 637.
14. Dursch, G., Med. Mschr., 1952, Vol. 6, page 666.
15. Edens, E., Klin. Wschr., 1936, Vol. 15, page 1829.
16. Fromherz, K., Welsch, D., Arch. f. exper. Path. u.

Pharmakol., 1931, Vol. 161, page 266.

17. Karrer, B., Helvet. chim. acta, 1929, Vol. 12, page 506.

18. Kodejszko, E., Czernik, A., Polsk. arch. med. wewn., 1954, Vol. 24, page 39.

19. Schmitz, W., Ztschr. f. Kreislaufforsch., 1953, Vol. 42, page 892.

20. Starr, I., Circulation, 1954, Vol. 9, page 664.

21. Wenckebach, K., Wien. med. Wschr., 1930, Vol. 80, page 325.

Received 18 May 1959

1288 END